CLAIMS

WHAT IS CLAIMED IS:

1.   A method for screening a plurality of test substances useful for the prevention or treatment of a disease involving an oxidative stress, which comprises the steps of

     i) testing each of the test substances for its ability to inhibit the activity of GADD34L and

     ii) identifying the test substance which inhibits the activity of GADD34L, thereby to identify a test substance useful as a preventive or therapeutic agent for a disease involving an oxidative stress.

2.   A method for identifying a test substance useful for the prevention or treatment of a disease involving an oxidative stress, which comprises testing a test substance for its ability to inhibit the activity of GADD34L, thereby to determine whether the substance promotes resistance to cell stress, and to identify said substance as a preventive or therapeutic agent for a disease involving an oxidative stress.

3.   The method according to claim 1 or 2, wherein the test substance inhibits the activity of the GADD34L protein by disrupting formation of the GADD34L and PP1c protein complex.

4.   The method according to claim 1 or 2, wherein the test substance inhibits the activity of GADD34L by inhibiting the production of GADD34L protein from the GADD34L mRNA.

5.   The method according to claim 1 or 2, wherein the test substance inhibits the activity of GADD34L by inhibiting the production of GADD34L mRNA from the GADD34L genomic locus.

6.   The method according to claim 2 or 3, further comprising a step of verifying whether said test substance does not cause stress to cells.

1	7. The method according to claim 1 or 2, which comprises the steps of
2	i) contacting the test substance or each of the test substances with a cell-
3	free composition containing GADD34L and PP1c proteins in the form of a purified
4	complex and eIF2α in a phosphorylated form,
5	ii) assessing the level of phosphorylation of eIF2α, in comparison with
6	the level of phosphorylation determined in the absence of test substances, in a cell-
7	free composition containing GADD34L and PP1c proteins in the form of a purified
8	complex and eIF2α in a phosphorylated form, and
9	iii) identifying the test substance which provides a higher level of
10	phosphorylation of eIF2α, in comparison with the level of phosphorylation
11	determined in the absence of test substance, thereby to identify a test substance useful
12	as a preventive or therapeutic agent for a disease involving an oxidative stress.
1	8. The method according to claim 7, wherein the assessment of the level of
2	phosphorylation of eIF2α is effected by an immunoassay using an antibody that
3	specifically recognizes the phosphorylated form of eIF2α.
1	9. The method according to claim 7, wherein the assessment of the level of
2	phosphorylation of eIF2α is effected by tracking the covalent binding of a
3	radiolabelled phosphate group to eIF2α.
1	10. The method according to claim 1 or 2, which comprises the steps of
2	i) contacting a test substance or each of the test substances with cells not
3	subject to stress that contain PP1c and eIF2α and that overexpress GADD34L, or
4	portions thereof,
5	ii) assessing the level of phosphorylation of eIF2α after contact with the test
6	substance or test substances, in comparison with the level of eIF2α phosphorylation
7	in the absence of test substances, and
8	iii) identifying the test substance which provides a higher level of
9	phosphorylation of eIF2α, in comparison with the level of phosphorylation
10	determined in the absence of test substance, thereby to identify a test substance useful
11	as a preventive or therapeutic agent for a disease involving an oxidative stress.

1   11.   The method according to claim 10, wherein the assessment of the level of
2   phosphorylation of eIF2α is effected by an immunoassay using an antibody that
3   specifically recognizes the phosphorylated form of eIF2α.

1   12.   The method according to claim 10, wherein the assessment of the level of
2   phosphorylation of eIF2α is effected by tracking the covalent binding of a
3   radiolabelled phosphate group to eIF2α.

1   13.   The method according to claim 1 or 2, which comprises the steps of,

2   i)   contacting a test substance or each of the test substances with cells that
3   normally express endogenous GADD34L,

4   ii) and identifying a test substance that inhibits the expression of endogenous
5   GADD34L, thereby to identify a test substance useful as a preventive or therapeutic
6   agent for a disease involving an oxidative stress.

1   14.   The method according to claim 13, wherein the level of GADD34L
2   expression is assessed by determining the level of transcription of GADD34L.

1   15.   The method according to claim 14, wherein determination of the level of
2   transcription of GADD34L is effected by means of a Northern blot.

1   16.   The method according to claim 14, wherein determination of the level of
2   transcription of GADD34L is effected by means of *in situ* hybridization.

1   17.   The method according to claim 13, wherein the level of GADD34L
2   expression is assessed by the level of translation of GADD34L.

1   18.   The method according to claim 17, wherein determination of the level of
2   translation of GADD34L is effected by means of an immunoassay.

1   19.   The method according to claim 1 or 2, which comprises the steps of

2   i)   contacting a test substance or each of the test substances with cells not
3   subject to stress that overexpress GADD34L, or portions thereof,

4   ii) assessing the expression of expression of a target gene, and

5   iii) identifying a test substance that activates the expression of the target gene,

6   thereby to identify a test substance useful as a preventive or therapeutic agent for a

7   disease involving an oxidative stress.

1   20.   The method according to claim 19, where the target gene is the CHOP

2   gene.

1   21.   The method according to claim 1 or 2, which comprises the steps of,

2   i) obtaining cells not subject to stress that overexpress GADD34L, or

3   portions thereof, and have been transfected with a reporter gene operatively

4   associated with all or part of the promoter of a target gene,

5   ii) contacting a test substance or each of the test substances with these cells,

6   and assaying the level of expression of said reporter gene, and

7   iii) identifying a test substance that activates the expression of the reporter

8   gene, thereby to identify a test substance useful as a preventive or therapeutic agent

9   for a disease involving an oxidative stress.

1   22.   The method according to claim 21, where the target gene is the CHOP

2   gene.

1   23.   The method according to claim 21, wherein said reporter gene encodes

2   one of the group consisting of GFP, CAT, GAL, LUC, and GUS.

1   24.   The method according to claim 1 or 2, which comprises the steps of,

2   i) obtaining cells not subject to stress that overexpress GADD34L, or

3   portions thereof,

4   ii) contacting a test substance or each of the test substances with the cells, in

5   the presence of a toxic agent that induces oxidative stress,

6   iii) quantitating cell survival of the cells that overexpress GADD34L, or

7   portions of GADD34L, following exposure to the toxic agent in the presence and

8   absence of test substances, and

9   iv) identifying a test substance that promotes cell survival of the cells

10   following exposure to concentrations of toxic agent that induce oxidative stress,

11   thereby to identify a test substance useful as a preventive or therapeutic agent for a

12   disease involving an oxidative stress.

1   25.   The method according to claim 24 wherein the toxic agent which induces

2   oxidative stress is tunicamycin, arsenite, or glutamate.

1   26.   The method according to claim 1 or 2, wherein the identified test

2   substance is useful for the prevention or treatment of a disease involving neuronal

3   ischemia.

1   27.   The method according to claim 1 or 2, wherein the identified test

2   substance is useful for the prevention or treatment of a disease involving heart

3   ischemia.

1   28.   The method according to claim 1 or 2, wherein the identified test

2   substance is useful for the prevention or treatment of renal damage induced by

3   ischemia or toxins.

1   29.   The method according to claim 1 or 2, wherein the identified test

2   substance is useful for the prevention or treatment of an auto-immune disease.

1   30.   The method according to claim 1 or 2, wherein the selected compound is

2   useful for the prevention or treatment of a neurodegenerative disorder.

1   31.   A method for the prevention or treatment of a disease involving an

2   oxidative stress in a patient in need of such treatment, which comprises administering

3   to the patient an effective amount of a GADD34L inhibitor identified for its ability to

4   promote resistance to cell stress while not causing stress.

1   32.   A method of claim 31, wherein the disease is a disease involving neuronal

2   ischemia, a disease involving heart ischemia, a disease involving renal damage

3   induced by ischemia or toxins, an auto-immune disease, or a neurodegenerative

4   disorder.